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# Routine versus As-Needed Bevacizumab with 12-Weekly Assessment Intervals for Neovascular Age-Related Macular Degeneration

## 92-Week Results of the GMAN Trial

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**Purpose:** To evaluate the efficacy and safety of intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA) in patients with neovascular age-related macular degeneration (nAMD) using 2 different treatment regimens in which patients were assessed clinically at up to 12-week intervals.

**Design:** Randomized, controlled, noninferiority trial.

**Participants:** A total of 331 patients with nAMD.

**Methods:** Patients were treated with 1.25 mg intravitreal bevacizumab and followed up to 92 weeks. They were randomized into 2 arms. All patients received 3 loading doses 4 weeks apart and thereafter were assessed every 12 weeks until the end of the study. One arm received a routine treatment at each 12-week assessment, and the other arm was treated at these assessments on an as-needed basis. After the loading doses, patients in either arm who showed signs of disease activity had an additional assessment after 6 weeks and at that visit had top-up treatments on an as-needed basis.

**Main Outcome Measures:** Mean best-corrected visual acuity (BCVA) at 92 weeks.

**Results:** At 92 weeks, patients who had treatments every 12 weeks had superior BCVA to those treated on an as-needed basis every 12 weeks ( $P = 0.008$ ), with the regular treatment arm gaining a mean BCVA of 5.5 letters and the as-needed treatment arm gaining 0.6 letters. The regular treatment arm of the study showed significantly improved outcomes with respect to 5-, 10-, and 15-letter changes in BCVA from baseline compared with the as-needed treatment arm, as well as superior reading speed. In patients who completed the study, up to but not including week 92, the mean number of treatments was 10.8 for the regular treatment arm and 9.1 for the as-needed treatment arm.

**Conclusions:** A treatment regimen with regular bevacizumab injections every 12 weeks after loading doses supplemented with as-needed top-up treatments produced a stable improvement in BCVA from baseline. The improvement in BCVA was broadly similar to that obtained in other studies using anti-vascular endothelial growth factor drugs with more frequent assessments and treatments. *Ophthalmology* 2015;122:1348-1355 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



\*Supplemental material is available at [www.aaojournal.org](http://www.aaojournal.org).

Neovascular age-related macular degeneration (nAMD) is one of the leading causes of blindness in the western world,<sup>1</sup> and vascular endothelial growth factor (VEGF) is an important agent in its pathogenesis. In 2006, landmark trials demonstrated a profound impact of monthly injections of the anti-VEGF agent ranibizumab (Lucentis; Genentech, South San Francisco, CA) on patients with nAMD, heralding a surge of interest in the treatment of this condition and in anti-VEGF agents.<sup>2,3</sup> Aflibercept (Eylea;

Bayer/Regeneron, Tarrytown, NY) is a more recent anti-VEGF therapeutic with a higher affinity for VEGF, and its use in clinical trials has demonstrated noninferiority in visual outcomes to monthly ranibizumab injections, despite only being injected every 2 months after the first loading dose phase.<sup>4</sup> As well as ranibizumab and aflibercept, many ophthalmologists globally use bevacizumab (Avastin, Genentech) off-label, which is a less-expensive anti-VEGF alternative<sup>5</sup> and has demonstrated noninferiority of visual

outcomes compared with ranibizumab in large, randomized controlled trials.<sup>6–9</sup>

Delivery regimens for each of these agents varies; treatment by monthly injections has been used as a gold standard strategy for visual outcomes in comparison trials, but is rarely followed in clinical practice, with most physicians opting for less frequent injection regimens using as-needed treatments, or regimens whereby treatment intervals are varied according to disease activity. Service providers and clinicians need to consider economic, capacity, and convenience factors, as well as clinical efficacy and safety, when deciding on optimal treatments and treatment regimens for their patients. Thus, there is a need for pragmatic trials that compare alternative and less-intense treatment schedules.

The Greater Manchester Avastin for Neovascularisation (GMAN) study is such a trial, designed to compare the efficacy of a pro re nata (PRN) and regular (or ROUTINE) treatment regimen of bevacizumab for nAMD. Both study arms began with an injection every 4 weeks for the first 12 weeks and thereafter had evaluations every 12 weeks, with an option of an intermediate 6-week evaluation and treatment if there were signs of disease activity. Patients in the ROUTINE arm of this study received regular injections every 12 weeks at the scheduled visits, and patients in the PRN arm were treated at these scheduled visits on an as-needed basis when signs of disease activity were present. The study treatment regimens assessed patients on a less frequent basis than typically used in current practice.

## Methods

This was a single-center (Manchester Royal Eye Hospital, Manchester, UK), randomized, noninferiority trial comparing 2 different treatment regimens using bevacizumab for nAMD. It took place between February 2008 and May 2013. The trial was approved by a UK National Health Service Research Ethics Committee (07/H0206/57) and the UK government Medicines and Healthcare Products Regulatory Agency. It was registered with Current Controlled Trials (ISRCTN34221234) and the European Clinical Trials database (EudraCT number 2007-003853-97).

Full inclusion and exclusion criteria are listed in Table 1 (available at [www.aaojournal.org](http://www.aaojournal.org)). In brief, patients aged more than 50 years with a diagnosis of nAMD and a best-corrected visual acuity (BCVA) of logarithm of the minimum angle of resolution 0.3 to 1.2 were recruited. Patients were excluded if the lesion showed signs of >50% fibrosis, hemorrhage, or serous pigment epithelial detachment. Patients with a medical history of myocardial infarction, cardiovascular accident, or gastrointestinal perforation were excluded when the trial commenced. However, as more evidence emerged suggesting a low systemic risk from the intravitreal use of anti-VEGF drugs, the protocol was amended so that myocardial infarction and gastrointestinal perforation were not used as exclusion criteria, and only patients with a history of cerebrovascular accident within 6 months were excluded.

Participants were randomly assigned to 1 of 2 treatment arms. Computer-generated allocation lists were drawn up by the trial statistician using block randomization with a variable block size. Randomization was performed after patients had been successfully screened and recruited into the trial.

One eye of each of the recruited patients was included in the study. The patients in the study were treated with intravitreal injections of 1.25 mg of bevacizumab. The bevacizumab used in the

study was compounded by the pharmacy at the Royal Liverpool and Broadgreen University Hospitals NHS Trust (Liverpool, UK). The details of how this bevacizumab was prepared have been described.<sup>8</sup>

The assessments that were undertaken at each clinic visit are summarized in Table 2 (available at [www.aaojournal.org](http://www.aaojournal.org)). The optometrists who measured BCVA, reading speed, and contrast sensitivity were masked to the study arm; patients, treating clinicians, and other staff involved in the study were not masked.

The BCVA was measured using Early Treatment of Diabetic Retinopathy Study charts (Precision Vision, LaSalle, IL) at 2 m; 2 measurements were taken at each visit, and the result was averaged. Contrast sensitivity was determined with Pelli-Robson charts at 1 m as described previously.<sup>10</sup> Near vision visual function was measured using MNREAD Acuity Charts (University of Minnesota) at 40 cm with controlled lighting and optimized refraction, following the manufacturer's protocol.<sup>11</sup> This enabled calculation and graphical determination of critical print size, reading acuity, and maximum reading speed. Reading acuity (the smallest print size read correctly) was defined as  $1.4 - (\text{sentences read} \times 0.1) + (\text{number of words read incorrectly} \times 0.01)$ . Critical print size was the size of print at which reading speed first starts to decline from its maximum. Maximum reading speed was measured by the maximum number of words read per minute. These last 2 measurements were determined by plotting the time taken to read each sentence against sentence print size.

Central 1-mm macular thickness was measured by automated analysis on a Cirrus (Carl Zeiss, Oberkochen, Germany) optical coherence tomography (OCT) machine. Lesion morphology on recruitment to the study was assessed by the treating clinician after fluorescein angiography (FFA).

The study had PRN and ROUTINE treatment arms (Fig 1). The treatment regimen was the same in both study arms up to week 20; thereafter, the 2 arms differed. All patients received injections of bevacizumab at baseline and then at weeks 4 and 8. After week 8, all patients were evaluated every 12 weeks until the end of the study at week 92. From week 20 onward, patients in the PRN arm received treatment at each 12-week evaluation on an as-needed basis. Treatments were given if the lesion was deemed to be active by 1 or more of the following criteria: loss of  $\geq 5$  letters of vision since last visit, presence of subretinal fluid, increase in central retinal thickness of  $\geq 100$   $\mu\text{m}$  from thinnest recorded measurement, increase in lesion size by FFA, and new subretinal blood at edge of lesion. Treating clinicians were also given the option of giving bevacizumab treatments for other reasons, and these were recorded. From week 20 onward, patients in the ROUTINE arm received a regular injection of bevacizumab at 12-week intervals, irrespective of clinical signs. Patients in both arms of the study from week 8 onward were brought back for an interim assessment 6 weeks later if they had lost  $\geq 5$  letters of vision at the last scheduled visit, had subretinal fluid present, or had increased central retinal thickness of 100  $\mu\text{m}$  from the thinnest measurement. At the interim visit, the assessing clinician gave a top-up treatment if any of these signs were still present.

The protocol included an assessment of results at week 44 by the trial Data Monitoring and Ethics Committee to determine whether the study demonstrated sufficient efficacy and safety to continue into a second year. The Committee reported to the Trial Steering Committee that the study showed adequate efficacy and safety to proceed, but did not reveal the results of this interim analysis to the study investigators.

There was a protocol change during the study. In the initial protocol, patients who were in the ROUTINE arm, while being maintained in this arm, were switched to an as-needed treatment

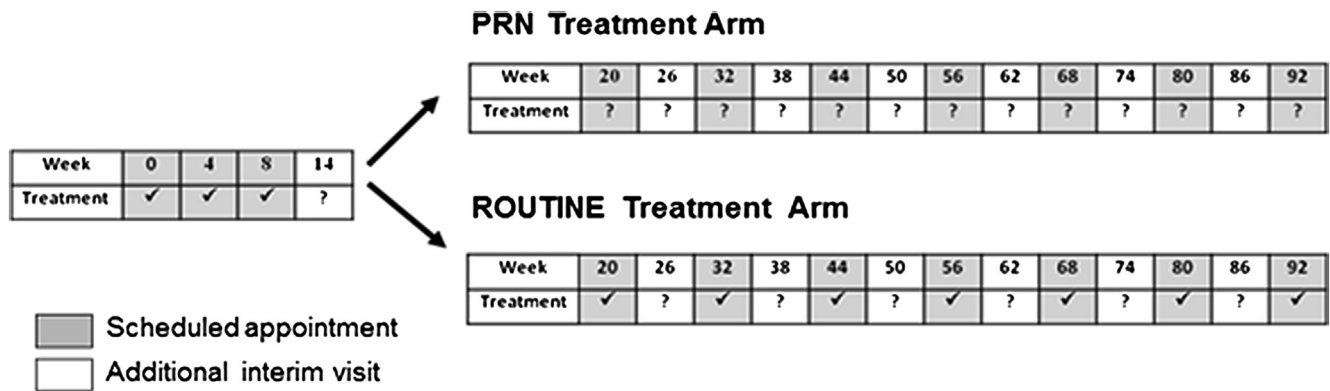


Figure 1. Overview of assessment and treatment schedules for the 2 study arms. PRN = pro re nata.

schedule if there had been no evidence of disease activity for 1 year. The protocol was changed during the study, and subsequently all patients in the ROUTINE arm were scheduled to have bevacizumab treatment at 12-week intervals whether there was disease activity or not. Before modifying the protocol, 9 patients in the ROUTINE arm who had had no disease activity for 12 months were converted to as-needed treatments, resulting in 17 treatments not being given to patients in the ROUTINE arm.

The primary end point outcome measure was mean BCVA at 92 weeks, with the trial designed to demonstrate that the PRN arm was not inferior to the ROUTINE arm with a noninferiority margin set at  $\leq 5$  letters. Prespecified secondary objectives included comparing change in mean visual acuity from baseline to 92 weeks and the percentages of patients who had a change in visual acuity from baseline of  $\geq 5$ ,  $\geq 10$ , or  $\geq 15$  letters. Other prespecified objectives included comparing contrast sensitivity, reading speed, and central macular thickness between the 2 arms at 92 weeks. The initial standard deviation of BCVA was estimated on the basis of pilot data to be 20, but after a masked review of the first 50 patients treated and follow-up for 5 months, this was found to be 12. This allowed for a noninferiority margin of 4 to 5 letters at 90% power for the sample size planned for the study (165 in each arm).

The primary analysis used a mixed model that assumes that the missing outcomes are “missing at random.” All visits  $\geq 20$  weeks (i.e., after treatments diverge) were included in the model with baseline outcome and baseline by visit interactions included as continuous variables, and visit and visit by arm interactions being included as factor variables. Because an unstructured covariance matrix was overspecified, a number of alternatives were explored and a banded structure was selected on the basis of the Akaike information criterion, which allowed for correlations between outcomes from the 4 visits for either group. Exploratory analyses confirmed that the results were not sensitive to the choice of correlation structure. A 2-sided 95% confidence interval (CI) estimate of the treatment effect was constructed from the model estimates to be used for interpretation of superiority or noninferiority. Numbers with positive or negative responses using alternative thresholds were tabulated and informally compared between groups using Fisher exact tests (i.e., no covariate adjustment). Although, given the design as a noninferiority study, intention-to-treat (all visits for all randomized participants) and per-protocol (patients who attended at least 75% of the scheduled treatment sessions) analyses were prespecified, as clear superiority was demonstrated, we present only the intention-to-treat results in this article.

## Results

A total of 331 patients were recruited to the study and randomized with 166 entering the PRN arm and 165 entering the ROUTINE arm (Fig 2). There were no substantial imbalances in the ocular or demographic characteristics between the 2 arms of the study (Table 3). During the study, 48 patients (14.5%) withdrew (26 in the PRN arm; 22 in the ROUTINE arm); consequently, 140 patients completed the study in the PRN arm, and 143 patients completed the study in the ROUTINE arm. The reasons for withdrawal included death/systemic illness in 33 patients, withdrawal of consent in 4 patients, loss to follow-up/moved out of area in 10 patients, and unable to assess visual acuity in 1 patient (Fig 2). Four patients, 2 per arm, were switched to ranibizumab during the study and then monitored on a 4-week basis. One patient in the PRN arm was switched to monthly assessments because of poor treatment response, and 1 patient in the ROUTINE arm had a retinal detachment and subsequently was treated on a PRN basis. No protocol deviations were recorded where patients met the criteria for as-needed treatment, but the treatment was not given. Other protocol deviations included 14 missed patient visits or treatments (6 in the PRN arm, 8 in the ROUTINE arm) and 128 patient visits (3.4% total; 3.7% PRN arm; 3.0% ROUTINE arm) taking place outside 1 week of the scheduled date in the first 3 monthly assessments or 2 weeks of the 12-week assessments.

The number of patients attending at each visit and the proportion treated are summarized in Table 4 (available at [www.aaojournal.org](http://www.aaojournal.org)). The proportion of patients in the PRN arm from week 20 onward who were treated at each 12-week assessment varied between 60.5% and 70.5% (mean, 65.4%). The proportion in the PRN arm who attended for additional interim assessments was between 38.0% and 41.1% (mean, 39.0%), and the proportion who were treated at these interim assessments was between 24.7% and 31.3% (mean, 27.7%). In the ROUTINE arm, between 23.8% and 44.4% (mean, 30.6%) of patients attended additional interim assessments at any particular time point, and at those interim assessments, between 17.5% and 33.8% (mean 23.2%) were treated. The reasons given for treating at scheduled visits in the PRN arm or at interim visits in either arm were similar (Table 5, available at [www.aaojournal.org](http://www.aaojournal.org)). The most common primary reasons were the presence of subretinal fluid (52% and 58% in the PRN and ROUTINE arms, respectively) and a decrease of  $\geq 5$  letters of vision (30% and 21% in the PRN and ROUTINE arms, respectively). Increased lesion size on FFA and new subretinal hemorrhage were given as reasons on less than 4% of occasions. On 6% and 13% of occasions, “other reasons” for treatment were

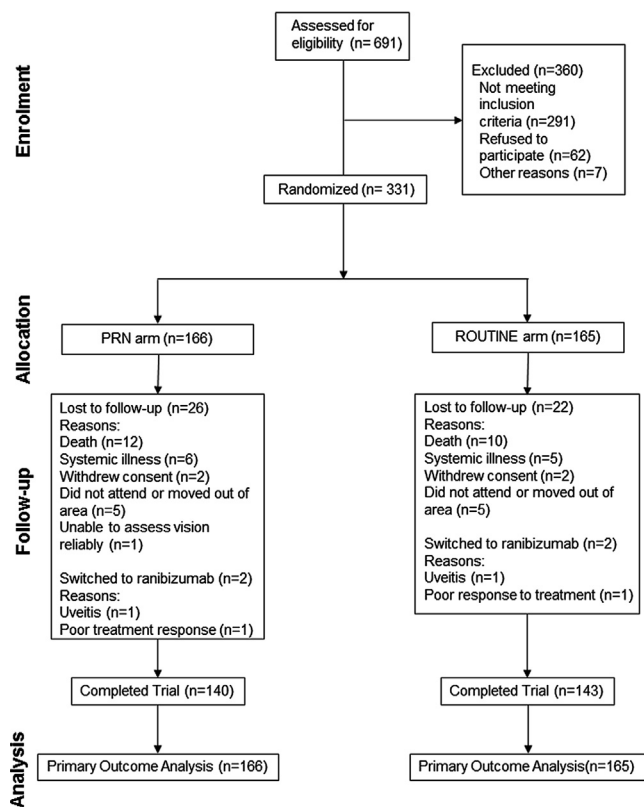


Figure 2. Flow diagram of patient participation. PRN = pro re nata.

given, and most often the reason given was an increase in central retinal thickness that had not reached 100  $\mu\text{m}$  greater than the thinnest measurement. In total, the mean number of treatments for patients completing the study was 10.8 for the ROUTINE arm and 9.1 for the PRN arm, excluding the last visit at weeks 92.

The primary outcome measure was BCVA at 92 weeks. There was no significant difference at week 20 (up to week 20, the treatment regimen was identical in both arms). At the end of the study (week 92), the ROUTINE arm was superior to the PRN arm ( $P = 0.008$ ) (Table 6). Compared with baseline, the patients in the PRN arm had a mean gain in visual acuity of 0.6 (95% CI,  $-2.0$  to  $3.1$ ) letters, whereas the ROUTINE arm had a mean gain of 5.5 (95% CI,  $2.9$ – $8.0$ ) letters at 92 weeks; the change in visual acuity over time is shown in Figure 3. By comparing the proportion of patients who gained or lost 5, 10, or 15 letters of vision over the course of the study, the ROUTINE arm was superior to the PRN arm by all measures (Fig 4). A higher number of patients in the PRN arm (22/168) lost vision of 20 letters or more between visits at some point during the study compared with the ROUTINE arm (8/165). This difference was statistically significant ( $P = 0.008$ , Fisher test).

Other outcome measures in the study included contrast sensitivity, reading speed, and central macular thickness measure using OCT. At 92 weeks, reading speed was superior in the ROUTINE arm compared with the PRN arm, but there was no significant difference in contrast sensitivity or central macular thickness between the 2 arms (Table 6).

Ocular adverse events (AEs) are summarized in Table 7 (available at [www.aaojournal.org](http://www.aaojournal.org)). One patient had a retinal detachment in the study eye, and 1 patient had a vitreous hemorrhage; both of these AEs were deemed to be probably related to the injection procedure. Five patients developed uveitis during the study. In 3 of these, it

Table 3. Patient Demographics and Baseline Characteristics

	PRN Arm	Routine Arm
Age, yrs		
Median (IQR)	80 (75–86)	80 (75–85)
Gender		
Female	62%	60%
Male	38%	40%
Ethnicity		
British/Irish white	97%	96.4%
Other white	2.4%	3%
Indian	0.6%	0%
Caribbean	0%	0.6%
BP systolic (mmHg)		
Median (IQR)	148 (135–160)	149 (134–161)
BP diastolic (mmHg)		
Median (IQR)	75.5 (69–82)	77 (70–83)
Intraocular pressure (mmHg)		
Median (IQR)	16.0 (15.0–18.0)	18.0 (15.0–20.0)
Lesion		
Predominantly classic	46%	59%
Minimally classic	19%	19%
Occult	34%	22%
logMAR study eye		
Median (IQR)	52.5 (44.0–64.0)	54.0 (40.0–63.0)
logMAR fellow eye		
Median (IQR)	68.0 (25.0–80.0)	68.0 (30.8–78.8)
Retinal thickness, mm (OCT)		
Median (IQR)	355 (310–464)	369 (326–488)

BP = blood pressure; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; OCT = optical coherence tomography; PRN = pro re nata.

was unilateral to the study eye and deemed to be probably related to bevacizumab treatment; 2 of these patients were switched to ranibizumab, and 1 of these patients was monitored but did not receive any further treatments in the study. In 2 other patients, the uveitis was bilateral and not thought to be related to the study drug. Other significant ocular AEs in the study eye included 2 retinal pigment epithelial tears in study eyes, and 24 patients (7.2%) underwent cataract surgery during the study; they were equally distributed between the 2 study arms.

A total of 113 nonocular systemic serious AEs were recorded during the study: 63 in the ROUTINE arm and 50 in the PRN arm (Table 7, available at [www.aaojournal.org](http://www.aaojournal.org)). These were classified as previously described.<sup>7</sup> There were 22 deaths in total, with 5 (1.5%) due to an arterial thrombotic event and 3 (1%) due to heart failure. There were no unexpected safety signals in the study.

## Discussion

Although this was designed as a noninferiority trial, it demonstrated that after 3 initial monthly doses of bevacizumab and 92 weeks of follow-up, a treatment regimen with fixed 12-week dosing (ROUTINE arm) was superior to 12-week, as-needed treatments (PRN arm), with both arms having additional as-needed interim treatments (Fig 1). At 92 weeks, the ROUTINE arm gained a mean visual acuity of 5.5 letters from baseline, whereas the PRN arm gained 0.6 letters. The PRN arm treatment regimen produced relatively poor results when compared with other trials



Table 6. Primary and Secondary Outcome Measures

Mean Best-Corrected Visual Acuity at Baseline, Week 20, and Week 92					
Outcome	Visit (Week)	PRN Mean (SD)	Routine Mean (SD)	Effect (CI) Routine - PRN	P Value
BCVA (logMAR)	0	52.7 (12.7)	51.5 (13.5)		
	20	56.1 (16.6)	56.6 (16.3)	1.7 (−0.82 to 4.2)	0.187
	92	52.8 (19.4)	57.2 (17.6)	4.8 (1.2–8.3)	0.008

Contrast Sensitivity, Reading Speed, and Central Macular Thickness at Baseline and Week 92					
Outcome	Week	PRN Mean (SD)	Routine Mean (SD)	Effect (CI) (Routine-PRN)	P Value
Contrast sensitivity (Pelli-Robson)	0	21.7 (5.9)	21.6 (5.5)		
	92	20.5 (6.8)	21.8 (5.5)	1.2 (−0.048 to 2.4)	0.060
Reading speed	0	120.7 (65.9)	106.7 (67.0)		
	92	118.1 (70.3)	130.3 (68.2)	19.4 (5.1–33.8)	0.008
Central macular thickness (OCT)	0	386.5 (113.2)	394.7 (109.7)		
	92	272.4 (82.5)	263.9 (71.2)	−8.5 (−26.5 to 9.4)	0.35

BCVA = best-corrected visual acuity; CI = confidence interval; logMAR = logarithm of the minimum angle of resolution; OCT = optical coherence tomography; PRN = pro re nata; SD = standard deviation.

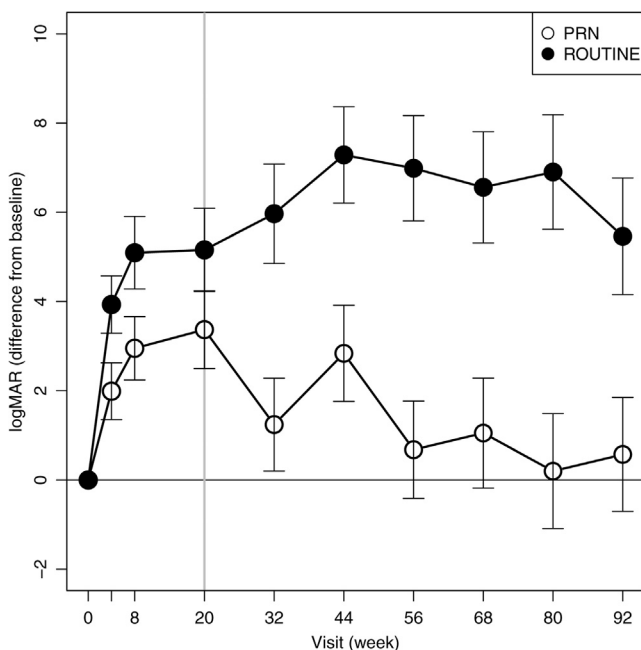
using bevacizumab over a similar time-frame on an as-needed basis, but with more frequent assessments.<sup>7,9</sup>

Smaller studies published before this trial commencing in February 2008 suggested that intravitreal bevacizumab may be an effective treatment for nAMD.<sup>12–14</sup> Since then, 2 large, randomized controlled trials, the Comparison of AMD Treatment Trials (CATT) and Inhibition of VEGF in Age-related

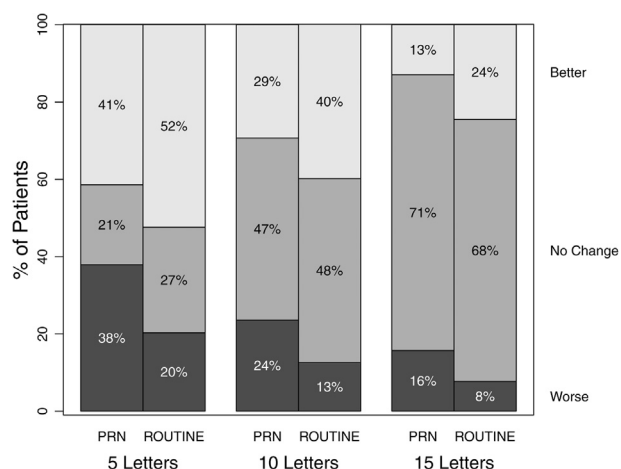
choroidal Neovascularization (IVAN) studies, have demonstrated noninferiority between ranibizumab and bevacizumab, whether given in routine monthly doses or using as-needed treatment schedules; both studies had 4-week assessments.<sup>7–9</sup>

The pivotal studies demonstrating the efficacy of ranibizumab (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD [ANCHOR] and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD [MARINA]) used 4-week assessments/treatments, and this is currently common practice,<sup>2,3</sup> albeit other studies have demonstrated that alternative regimens can be effective, such as treat-and-extend.<sup>15,16</sup> Hospital visits every 4 weeks can be a major burden for patients, their caregivers, and healthcare systems. The GMAN trial was undertaken to investigate less frequent assessment intervals using bevacizumab (1.25 mg); an assessment interval of 12 weeks was chosen, but adding an additional interim visit at 6 weeks for patients showing evidence of disease activity. The maximum number of visits in the study protocol was 17, and the maximum number of treatments was 16. In the PRN arm, the mean number of visits for patients who completed the study was 12.4 (mean number of treatments, 9.1). In the ROUTINE arm, the mean number of patient visits was 11.9 (mean number of treatments, 10.8). By comparison, in the CATT study over 104 weeks, the patients treated with the as-needed schedule received 14.1 injections of bevacizumab from a maximum of 26 possible injections (27 visits).<sup>7</sup> Over 92 weeks, patients being treated with aflibercept would expect to attend on 13 occasions.

Other studies have used ranibizumab with regular treatment regimens every 3 months. The year 1 results of the PIER study were published the same month that this study commenced.<sup>17</sup> In the PIER study, after 3 loading doses, ranibizumab was administered at 3-month intervals. After 1 year, the BCVA for patients receiving 0.3 mg ranibizumab was −1.6 letters from baseline, and after 2 years, BCVA



**Figure 3.** Change in visual acuity from baseline over course of study (error bars show standard errors of the unadjusted difference from baseline). Vertical line indicates the 20-week time point before which the 2 arms were treated identically. logMAR = logarithm of the minimum angle of resolution; PRN = pro re nata.



**Figure 4.** Change in best-corrected visual acuity (BCVA) from baseline of  $\geq 5$ ,  $\geq 10$ , or  $\geq 15$  letters at 92 weeks. The ROUTINE arm demonstrated superiority to the pro re nata (PRN) arm in all 3 measures:  $\geq 5$  letters,  $P = 0.005$ ;  $\geq 10$  letters,  $P = 0.030$ ;  $\geq 15$  letters,  $P = 0.010$  (Fisher exact test).

was  $-2.2$  letters from baseline<sup>18</sup>; by contrast, the ROUTINE arm of the GMAN study compares favorably with a 5.5-letter gain from baseline over 92 weeks. The EXCITE study lasted 12 months and compared monthly versus quarterly dosing with ranibizumab.<sup>19</sup> In this study, monthly dosing was superior to quarterly dosing, and the gain in visual acuity in the monthly dosing was 8.0 letters compared with 4.0 letters for quarterly dosing with 0.3 mg of ranibizumab. In the GMAN study, the ROUTINE arm at the equivalent time point (56 weeks) had a gain in vision of 7.0 ( $\pm 1.2$ ) letters. Therefore, with the caveat that cross-study comparisons have limitations, the ROUTINE treatment arm of the GMAN study did seem to produce better results than other 3 monthly dosing studies.

We believe that the main reason for the better results in the ROUTINE arm of the GMAN study than the PIER and EXCITE studies is the incorporation of the interim top-up treatments when there was disease activity. Treatment intervals of 3 months are likely to be too long in the presence of active disease. This also provides an explanation as to why the ROUTINE arm was superior to the PRN arm of the GMAN study despite there being only a modest difference in the mean number of treatments (10.8 vs. 9.1) because patients were not treated soon enough after reactivation of disease in the PRN arm. Our approach in the ROUTINE arm combines the benefits of regular treatments to stabilize disease (without risking overtreatment) and relatively long follow-up times, with additional top-up treatment to allow treatment to be tailored to individual patients.

A second potential reason why the results of the ROUTINE arm of the GMAN trial are better than those from the PIER or EXCITE studies is that bevacizumab has a longer half-life in the vitreous than ranibizumab.<sup>20,21</sup> However, ranibizumab does have higher binding affinity and being a smaller molecule has the potential for greater penetration of the retina.<sup>21,22</sup> A further possible reason is that the GMAN study protocol excluded lesions showing serous pigment epithelial detachment  $>50\%$  of the lesion.

This characteristic is associated with lesions that are harder to treat, such as idiopathic polypoidal choroidal vasculopathy and retinal angiomatous proliferation.

The GMAN study recorded the basis of as-needed treatment decisions. The presence of subretinal fluid was the primary reason given on more than 50% of occasions. A decrease in BCVA of  $\geq 5$  letters was the second most common reason, although this is not a reliable method given the variability of repeat responses observed,<sup>23,24</sup> and in routine clinical practice, this variability may be higher. The third most common reason was increased central retinal thickness of  $>100$   $\mu\text{m}$  from the thinnest measurement. This criterion was also used in earlier studies of PRN ranibizumab and could be 1 reason for inferior results versus monthly ranibizumab.<sup>25</sup> In the GMAN trial, investigators were allowed the flexibility of giving “other reasons” as an indication for treatment, and most commonly the reason given was an increase in retinal thickness of less than 100  $\mu\text{m}$ . In more recent studies, such as the CATT study, a “zero tolerance” of fluid approach was used to judge disease activity. The presence of new subretinal hemorrhage or increased lesion size on FFA was rarely given as a reason for treatment in the GMAN study, suggesting that these are not important criteria for making re-treatment decisions.

The GMAN study protocol had predefined re-treatment criteria for as-needed treatments, which were adhered to throughout the study. When intraretinal fluid was used as a re-treatment criterion, the protocol dictated that re-treatment should be given only if intraretinal fluid increased central retinal thickness by  $\geq 100$   $\mu\text{m}$  from the thinnest recorded measurement. In other recent studies such as CATT, the presence of any intraretinal fluid was used as a re-treatment criterion. If we had used this criterion in the GMAN study, the outcomes, especially in the PRN arm, might have been improved, and there may have been less of a difference between the study arms in outcomes. However, the difference between these trial protocols was partially offset by allowing GMAN investigators to treat at their own discretion if they thought the disease was active, but did not meet re-treatment criteria: The presence of intraretinal fluid that was less than 100  $\mu\text{m}$  from the thinnest recorded measurement was the most commonly given reason for doing this.

## Study Strengths and Limitations

This study was not powered to investigate safety and can only provide limited safety information because bevacizumab was used in both arms. However, no new safety signals emerged from the study. An important caveat is that the bevacizumab used in this study was provided by a compounding pharmacy that aliquoted and dispensed the drug, adhering to UK Medicines and Healthcare products Regulatory Agency standards. When less rigorous standards have been applied, serious AEs including endophthalmitis have emerged.<sup>26,27</sup>

A major advantage of bevacizumab is that it is more cost-effective than the licensed drugs ranibizumab and aflibercept,<sup>28–30</sup> and where there are no regulatory hurdles to its use, it provides an alternative therapeutic approach.

Use of a treatment schedule, such as the one used in the ROUTINE arm of this study with regular 12-week injections and interim treatments where necessary, could make bevacizumab even more cost-effective, and at the same time decrease the burden on patients and healthcare professionals of more frequent assessments and treatments.

A strength of the GMAN trial is its pragmatic design, with patients in the study being treated alongside nonstudy patients in a routine hospital setting. Limitations include the following: lack of a monthly assessment arm (which is regarded as the gold standard for comparative studies); not all lesion types were included; and because of financial constraints, there was no independent validation of clinical observations, angiography images, and automated OCT measurements by an external reading center. Although the PRN treatment arm produced inferior results, this study provides evidence that the ROUTINE protocol of regular treatments at 12-week intervals with bevacizumab and interim treatments when necessary is an effective way to manage nAMD.

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## Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

**AE** = adverse event; **BCVA** = best-corrected visual acuity; **CATT** = Comparison of AMD Treatment Trials; **CI** = confidence interval; **FFA** = fluorescein angiography; **GMAN** = Greater Manchester Avastin for Neovascularisation; **nAMD** = neovascular age-related macular degeneration; **OCT** = optical coherence tomography; **PRN** = pro re nata; **VEGF** = vascular endothelial growth factor.

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